REMARKS

Reconsideration of the above-identified patent application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled in this paper. Claims 1-8 have been amended in this paper. New claims 9-11 have been added in this paper. Therefore, claims 1-11 are pending and are under active consideration.

Claims 1-8 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> **Use Claims**: Claims 1-8 provide for the use of compounds of formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

In response to the above, Applicant has amended claims 1-8 so that claims 1-8 no longer are "use claims", but rather, are method claims that recite at least one active, positive step. Accordingly, the rejection has been overcome and should be withdrawn.

Claims 1-8 stand rejected under 35 U.S.C. 101. In support of the rejection, the Patent Office states the following:

> **Use Claims**: Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

For the same types of reasons given above in connection with the rejection under 35 U.S.C. 112, second paragraph, Applicant respectfully submits that the subject rejection has been overcome and should be withdrawn.

Claims 1-8 stand rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement. In support of the rejection, the Patent Office states the following:

> Should claims 1-8 be amended to recite methods, said claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating blood platelet aggregation, does **not** reasonably provide **enable**ment for a method of treating **myeloproliferative diseases**, and **brochodilation**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
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> ...
>
> **The breadth of the claims**: Claims 1-8 recite the use of compounds of formula I for treating myeloproliferative diseases and for bronchodilation. Although the scope is not unduly broad, such a use is not substantiated by the specification and state of the art.
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> **The amount of direction or guidance presented**: The specification provides an *in-vivo* assay. However, the assay result is indicative of the claimed formula I as a prodrug for Anagrelide (an imidazoquinazoline compound) which is not known to have bronchodilating activity. The assay is not directed to the compound's activity to treat myeloproliferative diseases or its activity on bronchodilation. Thus, the specification fails to provide enablement for the claimed activity.
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> **The state of the prior art**: As recognized by the specification, Jenks et al. (US 4,146,718) indicated that the compound of formula I can inhibit blood platelet aggregation. However, inhibiting platelet aggregation does not equate to treating myeloproliferative diseases, or bronchodilation. Thus, at best, the claimed compound can only reduce plaque, and increase circulation. Clearly, the treatment of myeloproliferative diseases, or bronchodilation is not supported by state of the art.

> As for Anagrelide (the active drug), while it appears to treat polycythemia vera and essential thrombocythemia (forms of myeloproliferative diseases), it can have severe cardiovascular side effects such as: myocardial infarction, complete heart block, atrial fibrillation, ect. as noted by Pescatore et al. (Expert Opinion on Pharmacotherapy, 2000, Vol. 1(3), pp. 537-546). Because of its side effects, Anagrelide is not the drug of choice in treating myeloproliferative diseases, and must be used with caution.
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> **The relative skill of those in the art:** Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given the complexity of myeloproliferative diseases alone, such a task would require a tremendous amount of effort, time and resource.
>
> **The predictability or unpredictability of the art & The quantity of experimentation necessary:** The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the *in-vivo* assay provided does not establish a structure-activity-relationship (SAR) for the claimed formula I in treating myeloproliferative diseases, or bronchodilation.
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> See **Hoffman v. Klaus** 9 USPQ2d 1657, and **Ex parte Powers** 220 USPQ 925 regarding type of testing needed to support in vivo uses.
>
> Thus, given the unpredictable nature of the art, and the complexity of the intended diseases, one skilled in the art will have to engage in undue experimentation to practice the method of treatment recited in claims 1-8. (Emphasis in original.)

Applicant respectfully traverses the subject rejection. As best understood by Applicant, the Patent Office is contending that claims 1-8 lack enablement "because the specification, while being enabling for a method of treating blood platelet aggregation, does not reasonably provide enablement for a method of treating myeloproliferative diseases, and bronchodilation." The Patent

Office's contention that the specification is not enabling for treating myeloproliferative diseases or for bronchodilation is apparently predicated on the Patent Office's position that anagrelide is not known to have activity in treating myeloproliferative diseases or in bronchodilation. For at least the reasons below, Applicant respectfully disagrees with the Patent Office's contention that the specification lacks enablement.

First of all, Applicant wishes to remind the Patent Office that it is the Patent Office who bears the burden of proof on the issue of enablement. The Patent Office must prove that the specification lacks enablement; Applicant need not prove the opposite. As a result, unless the Patent Office provides a well-supported basis upon which a person of ordinary skill in the art would reasonably believe that the uses asserted by Applicant are inoperable, such utilities must be presumed to be operable. Applicant need not dispel every conceivable doubt that may be raised by the Patent Office, regardless of how reasonable such a doubt may be.

Turning now to the case at hand, Applicant has disclosed in the present specification that the compounds of formula I represent a prodrug that is metabolized in vivo to yield anagrelide. In addition, Applicant has disclosed in the present specification that anagrelide has activity in treating myeloproliferative diseases and in bronchodilation. The Patent Office has provided no reasonable basis for doubting any of these statements. Instead, the Patent Office merely alleges, for example, that anagrelide "is not known to have bronchodilating activity." However, this allegation is not supported by any evidence. In fact, to the contrary, U.S. Patent No. 4,146,718 ("Jenks et al."), which is relied upon by the Patent Office later in the outstanding Office Action, specifically teaches at col. 1, lines 63-65 thereof that anagrelide-type compounds are "bronchodilator agents." Similarly, the Patent Office's allegations regarding the activity of anagrelide with respect to myeloproliferative

diseases also lack support. The only evidence relied upon by the Patent Office to raise a question about the activity of anagrelide with respect to myeloproliferative diseases is Pescatore et al. However, Pescatore et al., instead of raising a reasonable doubt, actually supports Applicant's contention that anagrelide may be used to treat myeloproliferative diseases. In fact, Applicant notes that the title of Pescatore et al. is "Anagrelide: a novel agent for the treatment of myeloproliferative diseases." Moreover, Pescatore et al. specifically teaches, for example, at page 539, right column, first full paragraph, that "[a]nagrelide hydrochloride is an oral imidazoquinazoline compound for the treatment of MPD [myeloproliferative diseases]." Notwithstanding the above, the Patent Office appears to be taking the position that Pescatore et al. suggests that the risks associated with using anagrelide are so great as to outweigh its use. Applicant respectfully submits that such a position greatly overstates what is actually disclosed in Pescatore et al. Pescatore et al. clearly teaches, for example, at page 539, right column, first full paragraph, that the most frequent side effects of anagrelide are headache, nausea, heart palpitations, fluid retention and diarrhea. Although some more serious cardiovascular side effects are also noted in Pescatore et al., these side effects are said to be "rare" and appear to occur predominantly in patients with known or suspected heart disease. There is nothing in Pescatore et al. that substantiates the Patent Office's assertion that "Anagrelide is not the drug of choice in treating myeloproliferative diseases." In fact, the conclusion of Pescatore et al. reads as follows:

> Anagrelide hydrochloride is a quinazolin derivative that effectively decreases platelet numbers and maintains them at acceptable levels in patients with thrombocythaemia in various MPD. **Anagrelide is an effective first-line agent**, as well as a valid treatment option for thrombocythaemia in patients who are refractory to other therapies. Many patients develop side effects while taking anagrelide, **although these effects are relatively mild, occur early**

> **in treatment and resolve quickly**. The adverse events associated with anagrelide are different from other available therapies and many of its toxicities are related to its vasodilatory and positive inotropic effects. Because of this, it should be used cautiously in patients **with known or suspected cardiovascular disease**.
>
> Currently, anagrelide only has FDA approval for the treatment of ET, although its high specificity toward developing megakaryocytes, non-leukomogenic properties, and oral route of administration **make it a very attractive first line therapy [for] all MPD**. (Emphasis added.)

Consequently, given that Pescatore et al. explicitly teaches that anagrelide is an attractive first line therapy for all MPD, Applicant respectfully submits that the Patent Office's doubts regarding the safety of anagrelide are misplaced. The mere fact that Pescatore et al. advises that caution should be used in administering the drug to patients with cardiovascular disease does not mean that the drug should be regarded as unsafe.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-5, 7 and 8 stand rejected under 35 U.S.C. 102(b) "as being anticipated by Jenks et. al. (US 4,146,718)." In support of the rejection, the Patent Office states the following:

> In column 9, Example 1 describes a HBr salt of the compound of 5,6-Dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate, which is a tautomer form of a compound of the instant formula I with the following substituents:
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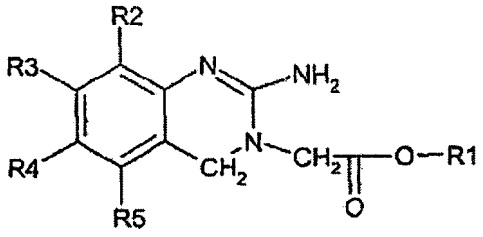
> i. R_1 is methyl;
> ii. R_2 and R_3 are hydrogen;
> iii R_4 and R_5 are Cl.
>
> The disclosed compound has blood platelet antiaggregative properties, and thus reads on the instant claims since the claim language is directed to producing pharmaceutical compositions in which the intended use does not have patentable weight.

Applicant respectfully traverses the subject rejection. Claim 1, from which claims 2-5

depend, has been amended in this paper and now recites "[a] method of producing a therapeutic agent for the treatment of myeloproliferative diseases and for bronchodilation in mammals comprising administering to a patient in need thereof an effective amount of a 2-amino-2H-quinazoline derivative of the general chemical formula I



(I),

wherein R1 is an alkyl group with 1-5 carbon atoms and R2, R3, R4 and R5, independently of one another, each indicate a chlorine or hydrogen atom, as well as their pharmaceutically compatible salts."

Jenks et al. neither anticipates nor renders obvious claim 1 for at least the reason that Jenks et al. does not teach or suggest, amongst other things, a method of producing a therapeutic agent that comprises administering to a patient a 2-amino-2H-quinazoline derivative of the general chemical formula I. In particular, nothing in Jenks et al. teaches or suggests that the compound referred to by the Patent Office, namely, 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydrobromide is, itself, administered to a patient.

Claim 7, from which claim 8 depends, is neither anticipated by nor rendered obvious over Jenks et al. for at least the same reasons given above in connection with claim 1. Additionally, nothing in Jenks et al. teaches or suggests combining a 2-amino-2H-quinazoline derivative of the general chemical formula I with at least one pharmaceutically compatible adjuvant. This is, in part,

because Jenks et al. does not contemplate converting the 2-amino-2H-quinazoline derivative into anagrelide in vivo.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

New claims 9-11 have been added in this paper. No new matter is added by these claims. Claim 9 is patentable over Jenks et al. because Jenks et al. does not teach or suggest combining a 2-amino-2H-quinazoline derivative of the general chemical formula I with at least one pharmaceutically compatible adjuvant. Claims 10 and 11 are patentable over Jenks et al. for at least the reason that Jenks et al. does not teach or suggest administering a 2-amino-2H-quinazoline derivative of the general chemical formula I to a patient.

In conclusion, it is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA D.C. 22313-1450 on August 29, 2007

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